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## (54) AMIDOXIME DERIVATIVES

(71) We, CHINOIN GYOGYSZER ES VEGYESZETI TERMEKEK GYARA RT., a body corporate organised under the laws of Hungary, of 1—5, To-utca, 1045 Budapest, Hungary, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new amidoxime derivatives and pharmaceutically acceptable salts thereof and to methods of preparing such compounds. In a further aspect this invention relates to pharmaceutical compositions comprising one or more of the above compounds of the invention. The compounds are of interest for treating diabetic angiopathy and in some instances hypertension in mammals. Some of the compounds of the invention show also $\alpha$-blocking activity.

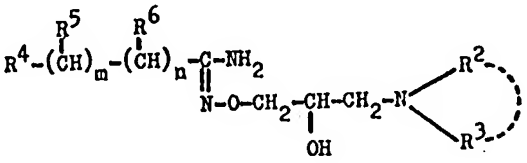
Diabetes mellitus is one of the most frequent metabolic diseases, and its main symptom is the disorganisation of the carbohydrate metabolism balance in the organism. This symptom is, however, often accompanied by pathological vascular disorders, for instance extremital vascular stenoses, pathological changes in the vessels of the retina, etc. At the present time there are numerous compounds known in the art, including insulin, for decreasing of hyperglycaemia but in the treatment of diabetic angiopathy, which is a concomitant disease, the results are very moderate when using the known, commercially available pharmaceutical preparations. The reason for this is that as a consequence of diabetes mellitus the adrenergic receptor sites of the vessels undergo essential changes, and therefore the adrenergic reactions induced by the pharmaceutical preparations in a diabetic are different from those in a non-diabetic organism [Nature New Biology, *243*, No. 130, 276 (1973); Szemészet, *111*, 23 (1974); Endocrinology, *93*, 752 (1973)]. Upon quantitative increase of the metabolism, the $\alpha$-adrenergic receptor sites of the vessels are transformed into $\beta$-receptors. The receptor transformation is due to a modulator compound [Amer. J. Physiol., *218*, 869 (1970)].When this compound is added to an $\alpha$-receptor the $\alpha$-antagonists are no longer effective since the receptor has been transformed into $\beta$-receptor. The original $\alpha$-sensitivity can be recalled by adding also a $\beta$-blocker.

In cases where a qualitative change appeared in the metabolism it has been found that the $\alpha$-antagonists (e.g. noradrenaline) preserve their activity but their effect can be inhibited by $\beta$-blockers. This is the first functional change appearing in a diabetic organism which can be detected already in about 24 hours after the administration of alloxan (hexahydrotetraketo-pyrimidine). The source of the

changes characteristic to diabetes is an imperfect $\alpha$-$\beta$ receptor transformation caused by the formation of an irregular modulator.

We have now discovered that certain amidoxime derivatives and pharmaceutically acceptable salts thereof show no or only a slight effect on the adrenergic reactions of the healthy vessels while having a strong influence on the adrenergic receptors which have undergone a pathological change due to the diabetes mellitus.

In summary the compounds of this invention can be represented by the general formula I



(I)

wherein:

$R^2$ is hydrogen or alkyl having one to five carbon atoms;

$R^3$ is alkyl having one to five carbon atoms, cycloalkyl or phenyl optionally substituted with hydroxyl or phenyl; or

$R^2$ and $R^3$ together may form a five- to eight- membered ring optionally containing also other heteroatoms and/or fused with another ring;

$R^4$ is cycloalkyl, or an aromatic or heteroaromatic group, optionally substituted with one or more halogens, alkoxy or alkyl groups and/or fused with another ring, preferably phenyl, naphthyl, quinolyl, isoquinolyl, pyridyl, pyrazolyl;

$R^5$ is hydrogen or alkyl having one to four carbon atoms, cycloalkyl or phenyl optionally substituted with halogen, alkoxy having one to four carbon atoms or alkyl having one to four carbon atoms;

m=0, 1 or 2;

n=0, 1 or 2;

$R^6$ is hydrogen, alkyl having one to four carbon atoms or phenyl.

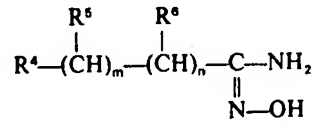
Also encompassed within the invention are pharmaceutically acceptable salts of the above compounds.

The compounds of the invention primarily show a selective $\beta$-blocking activity, and therefore may find their application in the treatment of diabetic angiopathy. Some of the compounds within the scope of the invention are also of interest as hypotensive agents and/or possess an $\alpha$-blocking activity.

Typical illustrations of the compounds of the general formula I, and salts thereof, are those described, hereinbelow in Examples 1 to 33. The preferred — $NR^2R^3$ group is the piperidino group, and the preferred $R^4$ substituents are phenyl or pyridyl substituted with an alkoxy. The particularly preferred compounds of the general formula I are: 0 - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethoxyphenyl - acetamidoxime dihydrochloride; and 0 - (3 - piperidino - 2 - hydroxy - 1 - propyl) - nicotinamidoxime dihydrochloride.

The compounds of the general formula I and the pharmaceutically acceptable salts thereof can be prepared by reacting

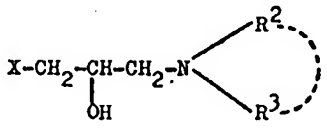
a) amidoximes of the general formula II



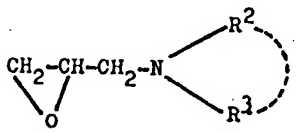
(II)

wherein:

$R^4$, $R^5$, $R^6$, n and m are as defined above, with amines of the general formula IIIA or IIIB



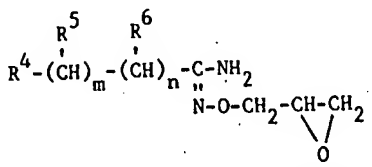
(IIIA)



(IIIB)

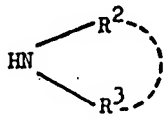
wherein $R^2$ and $R^3$ are as defined above, and X is halogen or other atom or group removable as an anion, in the presence of a base; or

b) amidoximes of the general formula II, wherein $R^4$, $R^5$, $R^6$, m and n are as defined above, with epichloro-hydrine, and reacting the amidoximes of the general formula V



(V)

initially obtained, with or without isolation, with amines of the general formula IV

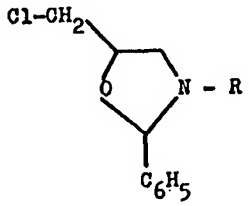


(IV)

wherein $R^2$ and $R^3$ are as defined above; or

c) the alkali metal salts of the amidoximes of the general formula II, wherein:

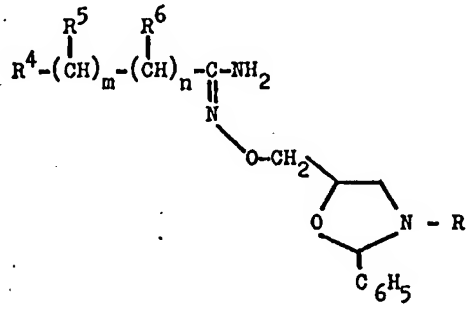
$R^4$, $R^5$, $R^6$, n and m are as defined above, with 2 - phenyl - 3 - substituted - 5 - chloromethyl - oxazolidines of the general formula VI



(VI)

wherein

R has the same meaning as given for $R^2$ and $R^3$ except hydrogen, and hydrolysing the compounds of the general formula VII



(VII)

without isolation;

said steps (a), (b) or (c) being optionally followed by transforming the compounds of the general formula I initially obtained into the pharmaceutically acceptable salts thereof with suitable organic or inorganic acids or setting free a base of the general formula I from the acid addition salts initially obtained.

The compounds of the general formula III can be prepared by reacting epichlorohydrin with amines in a manner known *per se*.

Procedure a) can preferably be effected by conducting the reaction in an aqueous medium; in an organic solvent containing water (e.g. in aqueous solution of alcohol); or in organic solvents, preferably at about from −10° or from 0° to 140°C.

One may instead react the amidoximes of the general formula II with alkali metal alcoholates in a dry medium, and add dropwise an alcoholic solution of the amines of the general formula III to the solution containing the amidoxime salts so

formed, The reaction is preferably carried out in the range from about 0° to 100°C, under stirring.

According to a further alternative the salts of the amidoximes of the general formula II are prepared with alkali metal hydroxides, preferably sodium or potassium hydroxide, in a non-water miscible organic solvent, e.g. benzene, toluene, xylene. The salt formation is effected at the boiling temperature of the solvent, the water liberated is removed from the system by azeotropic distillation, the solution of the amines of the general formula III is subsequently added and the reaction mixture is boiled for a further definite period.

According to a further embodiment of the process a) the reaction is performed in an aqueous medium, by adding an alkaline aqueous solution or suspension of the amidoximes to the compounds of the general formula III, under stirring. The reaction is preferably conducted in the range of about from 0° to 60°C, and the amidoxime is preferably dissolved or suspended in a 5 to 20% aqueous sodium hydroxide solution. The reaction can be accomplished also in an organic solvent—water mixture, for example by adding dropwise the alkaline aqueous solution or suspension of the amidoxime to an alcoholic or dioxane solution of a compound of the general formula III. The reaction can be carried out also in a reverse order, when the alkaline aqueous solution or suspension of the amidoxime the other compound is added.

According to the process b) of the invention amidoximes of the general formula II are reacted with epichlorohydrin in the presence of a base. If desired, the epoxide compound formed during the reaction can be isolated. It is, however, more convenient to effect the reaction in one step, without isolating the intermediate. The reaction may be carried out in an aqueuos or organic medium; in an organic solvent containing water; or in a two-phase solvent system, e.g. at a temperature as mentioned above or preferably of about from −10° to about +100°C.

According to an embodiment of this process the reaction is performed in an alkaline aqueous medium, by adding to the alkaline aqueous solution or suspension of the amidoximes 1 to 4 moles of epichlorohydrin. The addition of the epichlorohydrin is accomplished at −10° to +60°C, under stirring, in one or more portions, or by dropwise addition. The order of the addition can be reversed, either the alkaline aqueous solution or suspension of the amidoxime is added to the epichlorohydrin, or the amidoxime is added to the alkaline aqueous solution or suspension of the epichlorohydrin. The intermediate of the general formula V is optionally removed by extracting with a non water-miscible solvent. It is, however, more convenient to react the intermediates of the general formula V with the corresponding amines without previous isolation.

If the oxime starting substance is slightly soluble in the alkaline aqueous solution, the reaction can also be effected in an organic solvent containing water, e.g. in aqueous alcohols or aqueous dioxane. If desired, the reaction can be conducted also in a two-phase solvent system or in the presence of an emulsifying agent, by dissolving the epichlorohydrin in a non water-miscible organic solvent, for example in benzene or ether, adding the solution obtained to the alkaline aqueous solution or suspension of the amidoxime. The order of the addition of the reactants can be reversed also in this case.

The process b) of the invention can be effected also in dry solvents, preferably in dry alcohols. In this case an alkali metal salt of the amidoxime is prepared, preferably by dissolving the amidoxime in an alcohol solution of an alkali metal alcoholate. After the addition of the epichlorohydrin the reaction mixture is allowed to stand at 0° to 20°C for one to five days, whereupon a suitable amine is added and the reaction is conducted at room temperature or will heating of the reaction mixture. As dry solvents besides the alcohols also other organic solvents, for example acetone, dimethyl sulfoxide, dimethyl formamide etc. or the mixtures thereof can be employed.

When carrying out process c) as alkali metal salts of the amidoximes of the general formula II preferably sodium salts are used, and the reaction is preferably accomplished in alkanols. The hydrolysis of the intermediates of the general formula VII is preferably carried out with acids. The compounds of the general VI can be prepared by applying the procedure described in the West German OLS 2 018 263.

The products of the general formula I can be separated and purified according to conventional procedures, such as for example by crystallisation or extraction when an aqueous medium is used. If an organic solvent is employed, the product is

crystallized or the solvent is evaporated and the product is subsequently washed with water and dried. The products can be isolated also as their salts, or salts can be formed from the isolated bases by treating with one or two equivalents of a mineral acid or organic acid, preferably with pharmaceutically acceptable, non-toxic acids. Also the free bases can be liberated from compounds obtained as their salts. If desired racemic products can be resolved to obtain at least one optical isomer.

The compounds of the general formula I have been evaluated as general β-blockers by assay using trachearing preparations [J. Pharmacol. Exp. Therap., *90*, 104 (1974)] and papillary muscles of cats.

The assays of selective β-blocking activity on rat aorta-spiral preparations were carried out in the following way:

The thorax of the animal was opened and the thoracic aorta taken out and cut spirally. The motions of the straightened spiral were recorded with an isotonic recorder on two sooted cylinders. On the first cylinder the reactions of the control and on the second one the reactions of the rat-aorta treated with Streptozoticin[2 - (3 - nitroso - 3 - methyl - ureido) - 2 - desoxy - D - glucose] were recorded. The reaction was positive when the dose-effect curve of the noradrenaline was not influenced by the tested compound on the control preparation, while on the diabetic aorta the effect was inhibited. The compounds of the present invention generally showed a selective activity, which meant a strong β-blocking effect on diabetic aortae and no or slight effect on normal tests. Some of the tested compounds showed α-blocking activity on normal aortae.

Testing the product of the Example 2 [0 - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethoxyphenyl - acetamidoxime dihydrochloride] the following results were obtained:

The $pD_2$-values (negative logarithm of the dose corresponding to half of the maximum effect) were evaluated. The average of five subsequent tests calculated from the difference of the $pD_2$-values on diabetic aorta-spiral was $\bar{x}=1.31$. The corresponding value on normal spiral was $\bar{x}=0.52$. On guinea pig trachea 10γ of the tested substance decreased the effect of 0.01 γ/ml. isoprenaline [D,L - 1 - (3,4 - dihydroxyphenyl) - 2 - isopropyl - amino - ethanol] to half of its original level. On a rat uterus pretreated with Streptozotocin the tested compound had no effect when employed in a concentration of 100 γ/ml. In a concentration of 50 γ/ml. the tested compound set in motion the uterus preparation of the untreated rat, which was stopped by noradrenaline. This effect is identical with the effect of 0.5 μg/ml propranolol [1 - isopropylamino - 3 - (1 - naphthyloxy) - propane - 2 - ol]. On isolated strips of rat gastric fundus treated with Streptozotocin the tested compound showed no effect in a concentration of 10 γ/ml., in contrast to 0.01 γ/ml. of isoprenaline, where a relaxation of 25 mm. was observed. On isolated strips of rat gastric fundus which has not been pretreated even 100 γ/ml. concentration of the test compound had no effect on the dose—effect curve of isoprenaline, which means that it showed a strong β-blocking effect on diabetic samples and a slight effect on normal tests.

The hypoxia survival time was extended by one order of magnitude by the test compound.

The isoprenaline induced tachycardia was also slightly influenced by the tested compound. 5 minutes after the administration of a 10 mg./kg. i.v. dose the heart frequency increased by 10%, and 5 minutes after the administration of a 100 mg./kg. i.v. dose it decreased by 3%.

The tests carried out on the product of the Example 5 [0 - (3 - piperidino - 2 - hydroxy - 1 - propyl) - nicotamidoxime dihydrochloride] supplied the following results:

The mean-value calculated from the differences of the $pD_2$-values on diabetic aorta≠spiral was $\bar{x}=1.25$. The corresponding value in the control test was $\bar{x}=0.57$. The test compound used in a concentration of 50 γ/ml. decreased the effect of 0.001 γ/ml. isoprenaline from 16 mm. to 5 mm. When employed in a concentration of 100 γ/ml., it entirely compensated the effect of 0.001 γ/ml. isoprenaline, and decreased the effect of 0.01 γ/ml. isoprenaline from 28 mm. to 19 mm.

Tests were carried out to determine whether the noradrenaline induced contractions on the aorta≠spiral preparations of diabetic animals treated with Streptozotocin and untreated, respectively, could be compensated with propranolol. For control those animals were chosen, in which no receptor transformation took place. In case of the animals treated with Streptozotocin the mean difference between the $pD_2$-values (before and after the administration of propranolol) of the dose—effect curves of the noradrenaline were as follows:

$\bar{x}$=1.0335; $S\bar{x}$=0.0829; t=3.5885; p<0.01; n=8. On non-diabetic preparations the propranolol had no effect on the noradrenaline induced contractions.

Tests were carried out to evaluate if one can find a compound among the compounds structurally close to the β-blockers which has an effect on the aorta≠spiral of a diabetic animal similar to that of propranolol without exerting any substantial influence on the normal β-reactions. In other words a compound having a specific effect on the modified β-effect appearing in diabetic vessels was searched for. In the following test the compounds of the invention tested are as follows:

NP—18: 0 - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethyl - phenyl - acetamidoxime dihydrochloride

NP—51: 0 - (3 - piperidino - 2 - hydroxy - 1 - propyl) - nicotamidoxime dihydrochloride.

On the aorta-spiral of animals treated with Streptozotocin the difference between the $pD_2$-values before and after administrating a 1 μg./ml. dose of "NP—18" was: $\bar{x}$=0.6422; $S\bar{x}$=0.129; t=4.9783; p<0.01; n=6.

We found that if the initial receptor transformations are inhibited by adding compounds "NP—18" or "NP—51", the final histological changes do not occur. About 60% of the rats belonging to the CFY strain used during the tests were in a latent diabetic state which was detected in sugar-loading tests. On one group of these animals (weight=4 to 500 g.) diabetic macro- and micro-anigopathy was detected. In the animals which were treated with the compounds "NP—18" or "NP—51" at a weight of 200 g. the microangiopathy did not develop till they reached a weight of 500 g. and the degree of the macroangiopathy was also considerably smaller.

It was also found that although "NP—18" and "NP—51" inhibited the effect of isoprenaline on guinea pig trachea, they exerted an effect smaller by 4 orders of magnitude than propranolol. These compounds did not show any significant effect on the blood pressure, heart rate, minute volume and dp./dt. value of anesthesized cats. They did not influence the effect of isoprenaline in respect of the above parameters and caused bradychardia and dp./dt. decrease only in dose of 100 μg./kg. The effect was similar to that of 0.5 μg./kg. propranolol.

The difference between the β-blocking activity of the new compounds of the general formula I and the inderale on cat papillary muscle was also four orders of magnitude. They modified the effect on guinea pig ileum of barium chloride and acetylcoline only in a dose of 50 to 100 μg./ml. Neither the compound "NP—18" nor the compound "NP—51" had any influence on the hanging of mice on a rotating rod.

$LD_{50}$

NP—18: 165 mg./kg. i.v. mouse

NP—51: 123 mg./kg. i.v. mouse

The compounds of the general formula I and their pharmaceutically acceptable salts find their application in therapy in the form of pharmaceutical compositions in which the active ingredient is accompanied by the conventional pharmaceutical carriers or excipients. The compositions can be in the form of e.g. tablet, dragée, injection, capsule.

Further details of the invention are to be found in the following non-limiting Examples:

Example 1

2.3 g of sodium are dissolved in 200 ml. of abs. ethanol and 13.6 g. of benzamidoxime are added. The solution of 3 - piperidino - 2 - hydroxy - 1 - chloro - propane in 50 ml. of abs. ethanol—prepared from 9.3 g. of epichlorohydrin and 8.5 g. of piperidine in a manner known *per se*—is then added dropwise at the boiling temperature of the mixture. The reaction mixture is refluxed for eight hours, filtered, and the solvent is evaporated *in vacuo*. To the residue 100 ml. of 5% sodium hydroxide solution are added, and the oily product is extracted with benzene. Upon evaporating the benzene extract 9.2 g. of 0 - (3 - piperidino - 2 - hydroxyl - 1 - propyl) - benzamidoxime are obtained, melting at 97°C (from diisopropyl ether).

Molar weight: 277.35 ·

Elementary analysis:

| | | | |
|---|---|---|---|
| Calculated: | C=64.95%; | H=8.36%; | N=15.15%; |
| Found: | C=64.69%; | H=8.46%; | N=14.87%. |

The dihydrochloride salt of the product is precipitated from isopropanol solution by introducing hydrogen chloride or adding an alcohol solution of hydrochloric acid. Melting point: 212° to 214°C (isopropanol).
Molar weight: 350.29

Elementary analysis for $C_{15}H_{25}N_3O_2Cl_2$:
Calculated: $Cl^-$=20.24%;
Found: $Cl^-$=19.90%.

$LD_{50}$=70.5 mg./kg. i.v. on mice.

The nicotinic acid salt of the product obtained is prepared in abs. ethanol solution by adding petrol when the salt crystallizes. Melting point: 112°C (from methyl ethyl ketone).
Molar weight: 400.46

Elementary analysis for $C_{21}H_{28}N_4O_4$:
Calculated: C=62.98%; H=7.05%; N=14.00%;
Found: C=62.84%; H=7.11%; N=13.76%.

The dihydrochloride salt showed a slight $\alpha$-blocking activity on normal objects and a strong $\beta$-blocking activity on diabetic tests which were carried out as described in the introductory part of the specification.
$LD_{50}$=70.5 mg./kg. i.v. on mice.

Example 2

Following the procedure described in Example 1 but starting from 3,4 - dimethoxy - phenyl - acetamidoxime and 3 - piperidino - 2 - hydroxy - 1 - chloro - propane, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethoxyphenyl - acetamidoxime dihydrochloride is prepared. Melting point: 202° to 203°C (from abs. ethanol).
Molar weight: 424.38

Elementary analysis for $C_{19}H_{31}N_3O_4CL_2$
Calculated: C=50.94%; H=7.36%; N=9.90%; Cl=16.71%;
Found: C=50.80%; H=7.57%; N=9.84%; Cl=16.42%.
$LD_{50}$=165 mg./kg. i.v. (on mice)

On trachea-spiral and papillary muscle a slight $\beta$-blocking activity can be observed. The effect on papillary muscle at a temperature of 100 $\mu$g./ml. is identical with the effect caused by 0.05 $\mu$g./ml. of propranolol. On the gastric fundus in a concentration of 100 $\mu$g./ml. the compound does not have any influence on the activity of isoprenaline. At the aorta spiral of a diabetic animal, however, an inhibition of one order of magnitude had been observed.

Example 3

Following the procedure described in Example 1 but starting from 3,4 - dimethoxyphenyl - acetamidoxime and 3 - (1,2,3,4 - tetrahydro - 2 - isoquinolyl) - 2 - hydroxyl - 1 - chloro - propane, O - /3 - (1,2,3,4 - tetrahydro - 2 - isoquinolyl) - 2 - hydroxy - 1 - propyl/ - 3,4 - dimethoxyphenyl - acetamidoxime dihydrochloride is prepared. Melting point: 189°C (from isopropanol).
Molar weight: 472.40

Elementary analysis for $C_{22}H_{31}N_3O_4Cl_2$:
Calculated: C=55.93%; H=6.61%; N=8.89%; Cl=15.01%;
Found: C=55.89%; H=6.82%; N=8.64%; Cl=14.75%.

Example 4

Following the procedure described in Example 1 but starting from 3,3 - diphenyl - propionamidoxime and 3 - piperidino - 2 - hydroxy - 1 - chloro - propane, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime dihydrochloride is obtained. Melting point: 228° to 230°C (from isopropanol).

Elementary analysis for $C_{23}H_{33}N_3O_2Cl_2$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=60.79%; | H=7.32%; | N=9.25%; | Cl=15.60%; |
| Found: | C=60.45%; | H=7.25%; | N=8.94%; | Cl=15.79%. |

Example 5

Following the procedure described in Example 1 but starting from nicotinamidoxime and 3 - piperidino - 2 - hydroxy - 1 - chloro - propane, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - nicotinamidoxime dihydrochloride is prepared. Melting point: 204°C (from abs. ethanol).
Molar weight: 351.27

Elementary analysis for $C_{14}H_{24}N_4O_2Cl_2$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=47.87%; | H=6.89%; | N=15.95%; | Cl=20.19%; |
| Found: | C=47.59%; | H=7.00%; | N=15.64%; | Cl=19.89%. |

$LD_{50}$=123 mg./kg. i.v. (on mice). The product of this Example showed a slight β-blocking activity on normal test.

The nicotinic acid salt of the product is precipitated from ethyl acetate. Melting point: 111°C (from ethyl acetate).
Molar weight: 401.46

Elementary analysis for $C_{20}H_{27}N_5O_4$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=59.83%; | H=6.77%; | N=17.44%; | |
| Found: | C=59.80%; | H=6.92%; | N=17.23%. | |

$LD_{50}$=250 mg./kg. i.v. (on mice). The product shows a strong β-blocking activity on a diabetic aorta spiral.

Example 6

To 17.8 g. of 3 - piperidino - 2 - hydroxy - 1 - chloro - propane the solution of 10.45 g. of 3,4 - dimethoxyphenyl - acetamidoxime in 40 ml. of 10% sodium hydroxide—prepared with heating—is added dropwise in half an hour, at room temperature, under stirring. The reaction mixture is stirred at room temperature for eight hours and allowed to stand overnight. The oily product obtained is extracted with benzene, the extract is dried over sodium sulfate and the solvent is evaporated. From the ethyl acetate solution of the remaining 10.5 g. of O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethoxy - phenyl - acetamidoxime dihydrochloride crystallizes upon introducing hydrogen chloride. The product is identical with the product of the Example 2. Melting point: 201° to 203°C.

Example 7

To the benzene solution of 8.8 g. of 3 - piperidino - 2 - hydroxy - 1 - chloro - propane the solution of 5.2 g. of 3,4 - dimethoxyphenyl - acetamidoxime in 40 ml. of 10% sodium hydroxide solution—prepared under heating—is added dropwise, in half an hour at room temperature, under stirring. The reaction mixture is stirred at room temperature for further eight hours and allowed to stand overnight. The benzene phase is separated and the aqueous phase extracted with benzene. The benzene solution is dried over sodium sulfate and the solvent is evaporated. From the residue using the method set forth in Example 6 for preparation of the hydrochloric acid salt, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethoxyphenyl - acetamidoxime dihydrochloride salt is obtained. The compound is identical with the product of the Example 2.

Example 8

To 8.8 g. of 3 - piperidino - 2 - hydroxy - 1 - chloro - propane the solution of 5.2 g. of 3,4 - dimethoxyphenyl - acetamidoxime in 40 ml. of 10% sodium hydroxide solution and 40 ml. methanol is added under stirring, dropwise for half an hour, the mixture is stirred at room temperature for a further eight hours and allowed to stand overnight. After evaporating the methanol the extraction with benzene and the salt forming reaction is carried out as described in Example 7. O - (3 - piperidino - 2 - hydroxyl - 1 - propyl) - 3,4 - dimethoxyphenyl - acetamidoxime dihydrochloride is obtained which is identical with the product of the Example 2.

Example 9

To 2.72 g. of benzamidoxime 40 ml. of benzene and 0.8 g. of powdered sodium hydroxide are added. The reaction mixture is boiled for one hour under water

separator and 4.5 g. of 3 - piperidino - 2 - hydroxy - 1 - chloro - propane in 10 ml. of benzene are added to the boiling mixture dropwise. After boiling for 12 hours the solvent is evaporated and 20 ml. of 10% sodium hydroxide solution are added to the residue. The oily substance obtained is extracted with benzene and the benzene solution is evaporated. 3.6 g. of O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime are obtained. The compound is identical with the product of the Example 1.

Example 10

To a sodium ethylate solution prepared from 2.3 g. of sodium and 200 ml. of abs. ethanol 15.5 g. of 4 - chloro - benzamidoxime are added and subsequently 9.3 g. of epichlorohydrin are added dropwise at 0° to +10°C. The reaction mixture is stirred at 0° to +10°C for eight hours and allowed to stand overnight at this temperature. The sodium chloride precipitated is filtered off, to the filtrate 8.6 g. of piperidine are added under stirring dropwise and the mixture is stirred for a further eight hours at room temperature. The reaction mixture is heated to boiling point and the solvent is evaporated *in vacuo*. 50 ml. of 5% sodium hydroxide solution is added to the residue and the oily substance is extracted with benzene. The benzene solution is dried over sodium sulfate. evaporated and the residue dissolved in alcohol. Upon introducing hydrogen chloride or adding hydrochloric acid in alcohol 11.0 g. of O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 4 - chloro - benzamidoxime dihydrochloride are obtained. Melting point: 215° to 217°C (from abs. ethanol).
Molar weight: 384.73

Elementary analysis for $C_{15}H_{24}N_3O_2Cl_3$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=46.83%; | H=6.29%; | N=10.92%; | |
| Found: | C=46.57%; | H=6.41%; | N=10.58%. | |

The product shows a slight β-blocking activity on normal test and a strong β-blocking activity on diabetic test.

Example 11

Following the procedure described in Example 10 but starting from phenylacetamidoxime using diethyl amine as amine component O - (3 - diethylamino - 2 - hydroxyl - 1 - propyl) - phenylacetamidoxime dihydrochloride is prepared. Melting point: 156° to 158°C (from isopropanol).
Molar weight: 352.30

Elementary analysis for $C_{15}H_{27}N_3O_2Cl_2$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=51.14%; | H=7.73%; | N=11.93%; | Cl=20.12%; |
| Found: | C=50.89%; | H=7.65%; | N=11.83%; | Cl=20.10%. |

Example 12

Following the procedure described in Example 10 but starting from phenylacetamidoxime and using piperidine as amine component, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - phenylacetamidoxime dihydrochloride is obtained. Melting point: 198° to 200°C (from abs. ethanol).
Molar weight: 364.31

Elementary analysis for $C_{16}H_{27}N_3O_2Cl_2$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=52.75%; | H=7.47%; | N=11.54%; | Cl=19.47%; |
| Found: | C=52.40%; | H=7.51%; | N=11.20%; | Cl=19.85%. |

Example 13

Following the procedure described in Example 10 but starting from 4 - chlorophenyl - acetamidoxime and using morpholine as amine component, O - (3 - morpholino - 2 - hydroxy - 1 - propyl) - 4 - chlorophenyl - acetamidoxime dihydrochloride is obtained. Melting point: 175° to 178°C (from abs. ethanol).
Molar weight: 400.73

Elementary analysis for $C_{15}H_{24}N_3O_3Cl_3$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=44.96%; | H=6.04%; | N=10.48%; | Cl=26.54%; |
| Found: | C=45.20%; | H=6.10%; | N=10.52%; | Cl=26.50%. |

Example 14

Following the procedure described in Example 10 but starting from 3,3 - diphenyl - propionamidoxime and using isopropylamine as amine component, O - (3 - isopropyl - amino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime dihydrochloride is prepared. Melting point: 179°C (from acetone/water mixture).
Molar weight: 428.39

Elementary analysis for $C_{21}H_{31}N_3O_2Cl_2$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=58.87%; | H=7.29%; | N=9.81%; | Cl=16.55%; |
| Found: | C=58.58%; | H=7.39%; | N=9.53%; | Cl=16.70%. |

$LD_{50}$=16.25 mg./kg. i.v. (on mice). The compound possesses a strong β-blocking effect on diabetic aorta spiral.

Example 15

Following the procedure described in Example 10 but starting from 3,3 - diphenyl - propionamidoxime and using diethylamine as amine component, O - (3 - diethyl - amino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionaminoxime dihydrochloride is prepared. Melting point: 225°C (from isopropanol).
Molar weight: 442.42

Elementary analysis for $C_{22}H_{33}N_3O_2Cl_2$:

| | | | |
|---|---|---|---|
| Calculated: | C=59.72%; | H=7.52%; | Cl=16.03%; |
| Found: | C=59.68%; | H=7.55%; | Cl=16.07%. |

Example 16

Following the procedure described in Example 10 but starting from 3,3 - diphenyl - propionamidoxime and using 2 - methylamino - ethanol as amine component, O - [3 - N - methyl - N - (2 - hydroxy - ethyl) - amino - 2 - hydroxy - 1 - propyl] - 3,3 - diphenyl - propionamide dihydrochloride is prepared. Melting point: 175°C (from isopropanol).
Molar weight: 444.39

Elementary analysis for $C_{21}H_{31}N_3O_3Cl_2$:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=56.78%; | H=7.03%; | N=9.45%; | Cl=15.96%; |
| Found: | C=56.40%; | H=7.09%; | N=9.14%; | Cl=15.92%. |

$LD_{50}$=37 mg./kg. i.v. (on mice). The compound shows a strong β-blocking activity on diabetic aorta spiral.

Example 17

Following the procedure described in Example 10 but starting from 3,3 - diphenyl - propionamidoxime and using pyrrolidine as amine component, O - (3 - pyrrolidino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime dihydrochloride is obtained. Melting point: 218°C (from isopropanol).
Molar weight: 440.40

Elementary analysis for $C_{22}H_{31}N_3O_2Cl_2$:

| | | | |
|---|---|---|---|
| Calculated: | C=59.99%; | H=7.10%; | Cl=16.10%; |
| Found: | C=59.63%; | H=7.32%; | Cl=16.44%. |

Example 18

Following the procedure described in Example 10 but starting from 3,3 - diphenyl - propionamidoxime and using piperidine as amine component, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime dihydrochloride is prepared. The compound is identical with the product of the Example 4. Melting point: 228° to 230°C (from isopropanol).

Example 19

Following the procedure described in Example 10 but starting from 3,3 - diphenyl - propionamidoxime and using heptamethylene imine as amine component, O - (3 - heptamethyleneamino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - priopionamidoxime dihydrochloride is prepared. Melting point: 233°C (from isopropanol).
Molar weight: 482.48

Elementary analysis:
Calculated: C=62.24%; H=7.73%; Cl=14.70%;
Found: C=61.97%; H=7.70%; Cl=14.74%.

Example 20

Following the procedure described in Example 10 but starting from 3,3 - diphenyl - propionamidoxime and using morpholine as amine component, O - (3 - morpholino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime dihydrochloride is prepared. Melting point: 225°C (from isopropanol).
Molar weight: 456.40

Elementary analysis for $C_{22}H_{31}N_3O_3Cl_2$:
Calculated: C=57.89%; H=6.85%; N=9.20%; Cl=15.53%;
Found: C=57.66%; H=7.13%; N=8.95%; Cl=15.15%.

Example 21

Following the procedure described in Example 10 but starting from 1 - naphthyl - acetamidoxime and using diethyl amine as amine component, O - (3 - diethylamino - 2 - hydroxy - 1 - propyl) - 1 - naphthyl - acetamidoxime hydrochloride is prepared. Melting point: 150° to 152°C (from abs. ethanol).
Molar weight: 365.89

Elementary analysis for $C_{19}H_{28}N_3O_2Cl$:
Calculated: C=62.36%; H=7.71%; N=11.49%; Cl=9.69%;
Found: C=62.07%; H=8.00%; N=11.29%; Cl=9.63%.

Example 22

Following the procedure described in Example 10 but starting from 1 - naphthyl - acetamidoxime and using piperidine as amine component, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 1 - naphthyl - acetamidoxime hydrochloride is prepared. Melting point: 177° to 179°C (from abs. ethanol).
Molar weight: 377.89

Elementary analysis for $C_{20}H_{28}N_3O_2Cl$:
Calculated: C=63.57%; H=7.46%; N=11.12%; Cl=9.38%;
Found: C=63.58%; H=7.59%; N=11.47%; Cl=9.60%.

Example 23

To the mixture of 4.0 g. of benzamidoxime, 10 ml. of water and 4.5 g. of epichlorohydrin 20 ml. of 10% sodium hydroxide solution is added under stirring at room temperature dropwise, for one hour. The reaction mixture is then stirred for a further two hours, 4.5 g. of piperidine are added dropwise and stirring is continued for eight subsequent hours. The oily substance is extracted with benzene. Upon evaporating the benzene solution 6.2 g. of O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime are obtained. The compound is identical with the product of the Example 1.

Example 24

6.8 g. of benzamidoxime are dissolved in 40 ml. of 10% sodium hydroxide solution and 9.5 g. of epichlorohydrin are added under stirring. The reaction is exothermic, and therefore the temperature of the mixture is kept at 30° to 35°C by external cooling. After stirring for two hours 8.6 g. of piperidine are added dropwise. The mixture is stirred for a further two hours and the oily substance obtained is extracted with benzene. Upon evaporating of benzene 8.2 g. of O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime are obtained. The compound formed is identical with the product of the Example 1.

Example 25

6.8 g. of benzamidoxime are dissolved in 40 ml. of 10% sodium hydroxide solution and 9.5 g. of epichlorohydrin in 20 ml. of benzene are added under vigorous stirring dropwise. After stirring for four hours 8.6 g. of piperidine are added dropwise and the mixture is stirred at room temperature for a further eight hours. The benzene phase is separated and, the aqueous layer is extracted with benzene. Upon evaporating the combined benzene solutions O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime is obtained. This compound is identical with the product of the Example 1.

Example 26

6.8 g. of benzamidoxime are dissolved in the mixture of 20 ml. of 10% sodium hydroxide solvent and 20 ml. of methanol, and 9.5 g. of epichlorohydrin are added under stirring, dropwise. After stirring for two hours at room temperature 8.6 g. of piperidine are added dropwise and the stirring is continued for eight subsequent hours. The methanol is evaporated *in vacuo* and the oily substance is extracted with benzene. Upon evaporating the benzene solution 7.2 g. of O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime are obtained. This compound is identical with the product of the Example 1.

Example 27

To the solution of 5.2 g of 3,4 - dimethoxyphenyl - acetamidoxime in 20 ml. of dimethyl sulfoxide 2.4 g. of sodium tert-butoxide are added under stirring. 3.0 g. of epichlorohydrin are then added dropwise and the mixture is stirred at room temperature for two hours. Thereafter, the solution of 2.5 g. of piperidine in 60 ml. of acetone is then added and the reaction mixture is refluxed for eight hours, whereupon 120 ml. of ethyl acetate are added. Upon introducing hydrogen chloride 4.4 g. of O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethoxyphenyl - acetamidoxime dihydrochloride are obtained in crystalline form. This salt is identical with the product of the Example 2.

Example 28

Following the procedure of the Example 6 but starting from 2 - phenyl - propionamidoxime and 3 - piperidino - 2 - hydroxy - 1 - chloro - propane, O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - 2 - phenyl - propionamidoxime dihydrochloride are obtained. Melting point: 225°C (from isopropanol).

Elementary analysis:

| | | | | |
|---|---|---|---|---|
| Calculated: | C=53.96%; | H=7.73%; | N=11.11%; | Cl=18.74%; |
| Found: | C=54.27%; | H=8.00%; | N=10.86%; | Cl=18.45%. |

Example 29

Following the procedure described in Example 6 but starting from 3 - cyclohexylamino - 2 - hydroxy - 1 - chloro - propane (J. Org. Chem., *24*, 615/1959/) and nicotinamidoxime O - (3 - cyclohexylamino - 2 - hydroxy - 1 - propyl) - nicotinamidoxime is prepared. Melting point: 102°C (from the mixture of benzene and toluene).
Molar weight: 292.37

Elementary analysis for $C_{15}H_{24}N_4O_2$:

| | | | |
|---|---|---|---|
| Calculated: | C=61.62%; | H=8.27%; | N=19.16%; |
| Found: | C=61.44%; | H=8.23%; | N=18.89%. |

Example 30

1.38 g. of racemic O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime and 1.16 g. of d - camphorsulfonic acid are dissolved in 20 ml. of hot ethanol and the solution is evaporated *in vacuo*. The residue is recrystallized first from butyl acetate and then from ethyl acetate. 0.4 g. of d - O - (3 - piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime d-camphorsulfonate are obtained. Melting point: 132°C.

From the salt obtained the base is liberated by a conventional technique and the base obtained is transformed into a hydrochloride salt. The melting point of the hydrochloride salt is: 196°C.
$[\alpha]_{559nm}$=+6.3°(c=1%; water).

Example 31

1.15 g. sodium metal are dissolved in 100 ml. of abs. ethanol and 12.0 g. of 3,3 - diphenyl - propion - amidoxime are added. While boiling, there are added 13.2 g. of 2 - phenyl - 3 - isopropyl - 5 - chloromethyl - oxazolidine dropwise and the reaction mixture is boiled for a further 16 hours. The solvent is evaporated, 110 ml. of 5n hydrochloric acid solution are added to the residue and it is refluxed for one hour. The solution is extracted with ethyl acetate, decoloured with animal charcoal and adjusted to alkaline with 10% sodium hydroxide solution. The oily product is extracted with ethyl acetate, the extract is dried over dry sodium sulfate, and finally the solvent is evaporated. The residue is dissolved in acetone and the solution of hydrochloric acid in acetone is added. 7.0 g. of O - (3 - isopropylamino - 2 -

hydroxyl - 1 - propyl) - 3,3 - diphenylpropion - amidoxime dihydrochloride are obtained. This compound is identical with the product of the Example 14. Melting point: 179°C.

Example 32

Following the procedure of the Example 31 but starting from 2 - phenyl - propionamidoxime and 2 - phenyl - 3 - isopropyl - 5 - chloromethyl - oxazolidine O - (3 - isopropyl - amino - 2 - hydroxy - 1 - propyl) - 2 - phenyl - propionamidoxime dihydrochloride hemihydrate is obtained. Melting point: 168°C (from the mixture of acetone and isopropanol).
Molar weight: 361.31

Elementary analysis for $C_{15}H_{27}N_3O_2Cl_2 . 0.5\ H_2O$:
Calculated: C=49.86%; H=7.81%; N=11.63%; Cl=19.63%;
Found: C=49.79%; H=7.57%; N=11.61%; Cl=19.50%.

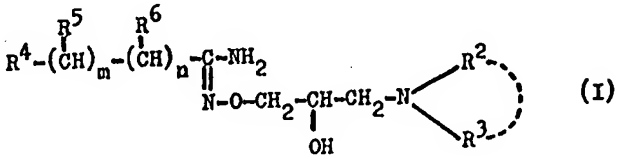
Example 33

Following the procedure described in the Example 31 but starting from benzamidoxime and 2 - phenyl - 3 - isopropyl - 5 - chloromethyl - oxazolidine O - (3 - isopropyl - amino - 2 - hydroxy - 1 - propyl) - benzamidoxime dihydrochloride hemihydrate is prepared. Melting point: 173° to 174°C.
Molar weight: 333.26

Elementary analysis for $C_{13}H_{23}N_3O_2Cl_2 . 0.5\ H_2O$:
Calculated: C=46.85%; H=7.26%; N=12.61%; Cl=21.28%;
Found: C=47.05%; H=7.13%; N=12.41%; Cl=21.54%.

WHAT WE CLAIM IS:

1. Compounds of the general formula I and pharmaceutically acceptable salts thereof



(I)

wherein:
$R^2$ is hydrogen or alkyl having one to five carbon atoms;
$R^3$ is alkyl having one to five carbon atoms, cycloalkyl or phenyl optionally substituted with hydroxyl or phenyl; or
$R^2$ and $R^3$ together form a five- to eight-membered ring optionally containing also other heteroatoms and/or fused with another ring;
$R^4$ is cycloalkyl, or an aromatic or heteroaromatic group, optionally substituted with one or more halogens, alkoxy or alkyl groups and/or fused with another ring;
$R^5$ is hydrogen or alkyl having one to four carbon atoms, cycloalkyl or phenyl optionally substituted with halogen, alkoxy having one to four carbon atoms or alkyl having one to four carbon atoms;
$R^6$ is hydrogen, alkyl having one to four carbon atoms or phenyl;
m=0, 1 or 2;
n=0, 1 or 2.

2. Compounds of claim 1 wherein $R^4$ is phenyl, naphthyl, quinolyl, isoquinolyl, pyridyl or pyrazolyl.

3. Compounds of claim 1 wherein $R^2$ and $R^3$ form together with the nitrogen they are attached to a piperidino group, $R^4$ is phenyl or pyridyl optionally substituted with one or two alkoxy groups each having one to four carbon atoms, and $R^5$, $R^6$, m and n have the meanings defined in claim 1.

4. The pharmaceutically acceptable salts of the compounds of claim 3.

5. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime and pharmaceutically acceptable salts thereof.

6. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - 3,4 - dimethoxy - phenyl - acetamidoxime and pharmaceutically acceptable salts thereof.

7. O - [3 - (1,2,3,4 - Tetrahydro - 2 - isoquinolyl) - 2 - hydroxy - 1 - propyl] - 3,4 - dimethoxyphenyl - acetamidoxime and pharmaceutically acceptable salts thereof.

8. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

9. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - nicotinamidoxime and pharmaceutically acceptable salts thereof.

10. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - 4 - chloro - benzamidoxime and pharmaceutically acceptable salts thereof.

11. O - (3 - Diethylamino - 2 - hydroxy - 1 - propyl) - phenylacetamidoxime and pharmaceutically acceptable salts thereof.

12. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - phenylacetamidoxime and pharmaceutically acceptable salts thereof.

13. O - (3 - Morpholino - 2 - hydroxy - 1 - propyl) - 4 - chloro - phenyl - acetamidoxime and pharmaceutically acceptable salts thereof.

14. O - (3 - Isopropylamino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

15. O - (3 - Diethylamino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

16. O - [3 - N - Methyl - N - (2 - hydroxyethyl) - amino - 2 - hydroxy - 1 - propyl] - 3,3 - diphenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

17. O - (3 - Pyrrolidino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

18. O - (3 - Heptamethyleneimino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

19. O - (3 - Morpholino - 2 - hydroxy - 1 - propyl) - 3,3 - diphenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

20. O - (3 - Diethylamino - 2 - hydroxy - 1 - propyl) - 1 - naphthyl - acetamidoxime and pharmaceutically acceptable salts thereof.

21. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - 1 - naphthyl - acetamidoxime and pharmaceutically acceptable salts thereof.

22. O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - 2 - phenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

23. O - (3 - Cyclohexylamino - 2 - hydroxy - 1 - propyl) - nicotinamidoxime and pharmaceutically acceptable salts thereof.

24. d - O - (3 - Piperidino - 2 - hydroxy - 1 - propyl) - benzamidoxime and pharmaceutically acceptable salts thereof.

25. O - (3 - Isopropylamino - 2 - hydroxy - 1 - propyl) - 2 - phenyl - propionamidoxime and pharmaceutically acceptable salts thereof.

26. O - (3 - Isopropylamino - 2 - hydroxy - 1 - propyl) - benzamidoxime and pharmaceutically acceptable salts thereof.

27. Compounds of claims 5—26 in the form of their salts with hydrochloric acid.

28. A compound of claim 1 as hereinbefore specifically disclosed excepting the compounds of claims 5—27.

29. Compounds of claim 1 substantially as illustrated in the Examples.

30. A pharmaceutical composition comprising at least one compound of claim 1 and a pharmaceutically acceptable carrier or excipient.

31. A composition of claim 30 comprising a compound of any of claims 2—4.

32. A composition of claim 30 comprising a compound of any of claims 5—27.

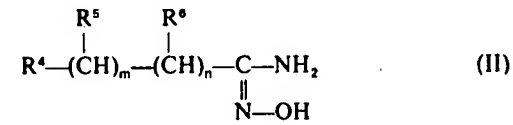
33. A composition of claim 30 comprising the compound of claim 6.

34. A composition of claim 30 comprising the compound of claim 9.

35. A composition of any of claims 30—34 in the form of dosage units.

36. A process for the preparation of a compound of claim 1 which comprises:

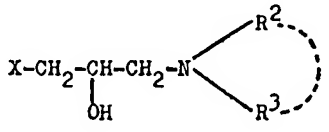
a) reacting an amidoxime of the general formula II



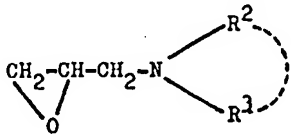
(II)

wherein:

$R^4$, $R^5$, $R^6$, n and m are as defined in claim 1, with an amine of the general formula IIIA or IIIb



(IIIA)

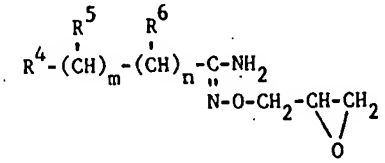


(IIIB)

wherein:

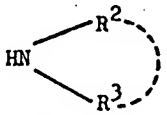
$R^2$ and $R^3$ are as defined in claim 1, and X is halogen or other atom or group removable as an anion, in the presence of a base; or

b) reacting an amidoxime of the general formula II defined above with epichlorohydrin, and reacting the amidoxime of the general formula V



(V)

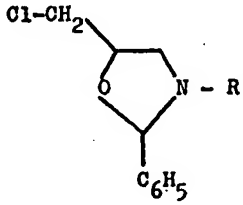
initially obtained, with or without isolation, with an amine of the general formula IV



(IV)

wherein $R^2$ and $R^3$ are as defined in claim 1; or

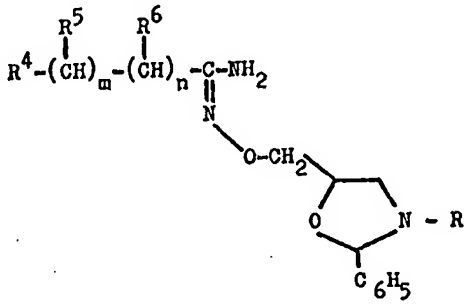
c) reacting an alkali metal salt of a compound of the general formula II defined above with a 2 - phenyl - substituted - 5 - chloromethyl - oxazolidine of the general formula VI



(VI)

wherein:

R has the same meaning as given for $R^2$ and $R^3$ except hydrogen, and subsequently hydrolysing the intermediate compound of the general formula VII



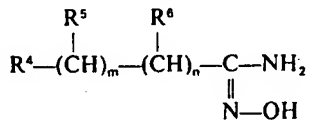
(VII)

without isolation.

37. A process according to claim 36 wherein said process a), b) or c) is performed in a reaction mixture containing a solvent selected from water, aqueous organic solvents and aqueous and organic solvent phases.

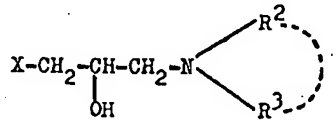
38. A process according to claim 36 or 37 wherein said process a), b) or c) is performed at a temperature of −10°C to +140°C.

39. A process for the preparation of a compound of claim 1 which comprises:
a) reacting an amidoxime of the general formula II

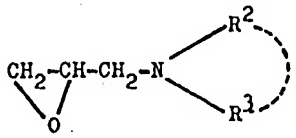


(II)

wherein:
$R^4$, $R^5$, $R^6$, n and m are as defined in claim 1, with an amine of the general formula IIIA or IIIB

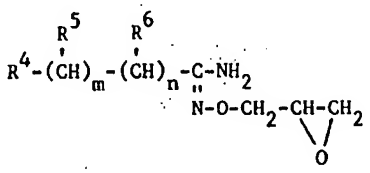


(IIIA)



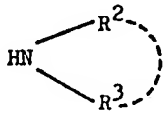
(IIIB)

wherein:
$R^2$ and $R^3$ are as defined in claim 1, and X is halogen, in the presence of a base;
or
b) reacting an amidoxime of the general formula II defined above with epichlorohydrin and reacting the amidoxime of the general formula V



(V)

initially obtained, after or without separation, with an amine of the general formula IV



(IV)

wherein $R^2$ and $R^3$ are as defined in claim 1.

40. A process according to claim 39 wherein said process a) or b) is performed in a reaction mixture containing a solvent selected from water, aqueous organic solvents and aqueous and organic solvent phases.

41. A process according to claim 39 or 40 wherein said process a) or b) is performed at a temperature of −10°C to +140°C.

42. A process according to any of claims 36—41 including the further step of transforming the product of general formula I initially obtained into a pharmaceutically acceptable salt thereof with a suitable organic or inorganic acid, or setting free a base of the general formula I from an acid addition salt thereof.

43. A process for the preparation of a compound according to claim 1, substantially as hereinbefore described.

44. A process for the preparation of a compound according to claim 1, substantially as hereinbefore described with reference to any of Examples 1 to 33, the product of the general formula I being optionally further transformed substantially as illustrated in any of the Examples.

45. A process according to any of claims 36—44 including the step of resolving a racemic product to obtain at least one optical isomer.

46. A compound of any of claims 1—26 in optically active form.

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